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September 18, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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MERCK Research Laboratories

Re:Docket No. 00D-1306 - FDA Draft Guidance for Industry on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (65 Federal Register 38563; June 21, 2000)

Merck & Co., Inc. is a leading worldwide human health product company. Merck's corporate strategy — to discover new medicines through breakthrough research — encourages us to spend more than $2 billion annually on worldwide Research and Development (R&D). Through a combination of the best science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical and biological products on the market today.

As a leading human health care company, Merck fully supports the concept of providing complete and up-to-date information regarding drug safety to the prescriber and presenting the information in a clear and accessible format through product labeling. This fundamental concept has been the standard used by Merck for all new labeling and updated labeling safety information submitted to the Agency for review and implementation.

For these reasons, Merck is very interested in, and well-qualified to comment on the proposed FDA Guidance for Industry on the Content and Format of the ADVERSE REACTIONS Section of Labeling for Human Prescription Drugs and Biologics.

Merck commends the Agency for developing this document and appreciates the opportunity to provide comments on this draft Guidance.

General Comments

1. The Draft Guidance does not specify if the proposed format for the ADVERSE REACTION section of labeling is to be applied only to new molecular entities or to encompass products already marketed.

   Merck Recommendation:
   Merck recommends this Guidance only be applied prospectively to new molecular entities that are the subject of New Drug Applications or new Biological License Applications. Products approved prior to finalization of the regulations/guidance on the ADVERSE REACTIONS section should be grandfathered. Any retroactive application of the final guidance for the ADVERSE REACTIONS section of labeling should be required only under special circumstances and with agreement between the manufacturer and the Agency, and would require a long lead-time for implementation (minimum of **five** years).

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If FDA would require all of these labeling changes to be submitted for review and approval, this period should be even longer, allowing time for industry to exhaust existing packaged and printed component inventory, and for the lead time required to make the change once the language was approved by FDA. Not allowing a long lead time to implement this change retroactively would impose a significant economic burden on companies; including, in some situations, the extra costs of modifying a company's packaging procedures and equipment to accommodate the additional space required within the package circulars.

2. The Draft Guidance does not specify if it will be part of the FDA's overall draft proposed regulation for revised content and format of prescription labeling, or if it is going to be implemented separately, before the issuance of the proposed regulation concerning new labeling format and content for professional labeling. It is Merck's position that it is inappropriate for FDA to use a guidance document to implement changes to any portions of the content and format of prescription drug labeling, the requirements of which are specifically enumerated in current FDA regulations (21 CFR 201.57). Moreover, Merck believes that some of the changes suggested in the draft Guidance are not consistent with the requirements of 21 CFR 201.57.

   Merck Recommendation:
   Merck recommends that the changes to the ADVERSE REACTIONS section of prescription drug labeling proposed in the Draft Guidance should be implemented only following the appropriate notice and comment procedures for proposed rule making (21 CFR 10.40). Alternatively, implementation of this Draft Guidance could be incorporated first into a broader proposed regulation concerning changes to content and format of professional labeling as a whole, following notice and comment rule making.

3. The Draft Guidance recommends inclusion of information such as medical interventions used to treat an adverse reaction. Merck does not agree for several reasons:
   - This type of information is not routinely captured in clinical trials. Thus, obtaining this information would require considerable re-engineering of the processes and procedures used by companies in clinical development programs and in post-marketing suspected Adverse Drug Reaction reporting.
   - Inclusion of such information reduces the importance of the medical judgment of the physician and subjects sponsors and physicians to legal action when physicians deviate from the labeling.
   - The practice of medicine is constantly changing and the standard of care varies geographically. It is neither appropriate nor possible for prescribing information to be a compendium concerning the practice of medicine. Additionally, the practice of medicine is not within FDA's jurisdiction.

   Merck Recommendation:
   Merck recommends, therefore, that this type of information not be included in the ADVERSE REACTIONS section of labeling.

4. The US Package Insert is both a medical and a legal document and existing product labeling for prescription drug products is the subject of substantial litigation regarding adequacy of warning.

Merck Recommendation:
The Agency should clarify and articulate explicitly that the initiative to provide new guidance on the ADVERSE REACTIONS section of labeling is based upon the premise that existing labeling can be improved, rather than that existing labeling is deficient.

5. The guidance does not specifically mandate a particular coding system, such as MedDRA.

   Merck Recommendation:
   Merck concurs with this approach and recommends that the Guidance not require a particular dictionary. However, with respect to specific terminology for reaction terms, Merck suggests that the Guidance specify that preferred level terms of the chosen coding system be used as the default so that a true adverse reaction is not obscured by multiple, similar terms.

6. The Draft Guidance recommends a specific format different from that currently in place be used when preparing an ADVERSE REACTIONS section of labeling.

   Merck Recommendation:
   It would be very helpful if FDA would provide a comprehensive example of the entire ADVERSE REACTIONS subsection within the Draft Guidance in both the "old" and "new" style, to enhance understanding of the proposed principles.

Specific Comments

Introduction

1. The draft Guidance addresses the need for greater consistency in content and format of the ADVERSE REACTIONS section of the label. Among other considerations for the inclusion of adverse reactions within the label, the Guidance states that, in general, the ADVERSE REACTIONS section should include only information that would be useful to clinicians when making treatment decisions and in monitoring and advising patients.

Merck Recommendation:
Merck recommends that this statement be clarified in conformance with labeling requirements as set forth in the Code of Federal Regulations (21CFR 201.57) to assure that it encompasses presentation of all adverse reaction data considered to be reasonably associated with the drug or biological product.

2. Further definition is required as to what is described as "useful information", i.e., those adverse reactions which are defined as adverse reactions where causality has been determined, along with adverse events based on a reasonable association to the drug, or just adverse reactions alone.

Merck Recommendation:
Merck recommends the concept of useful information be clearly defined and a plan articulated to assure that the information about this change is communicated to the health care practitioners.

ADVERSE REACTIONS Section - Content and Format

Section A - Overview - Content and Format

1. The Draft Guidance recommends inclusion of an "Overview" subsection within the ADVERSE REACTIONS section providing information on "serious and important" adverse reactions. Merck does not agree for the following reasons:
   - Implementing revisions such as an "Overview" subsection within the ADVERSE REACTIONS section would cause confusion for health care providers who routinely look for this type of information in other safety sections of the labeling, i.e., CONTRAINDICATIONS, PRECAUTIONS or WARNINGS.
   - An Overview subsection would place too much emphasis on some adverse reactions while potentially downplaying, in the minds of physicians, the importance of others.
   - Additionally, the assessment of which terms should be included within such a subsection would be based on individual judgment and result in decreased uniformity in product labeling rather than meeting FDA's desired outcome of increased consistency in product labeling.

Merck Recommendation:
Merck recommends that an Overview subsection not be included within the ADVERSE REACTIONS section of the labeling.

2. The Draft Guidance recommends the Overview contain listings of ... "serious and important adverse reactions...." There is no definition of "important" in current regulations. Prior to implementing any guidance document, FDA should establish a regulatory definition of "important adverse reactions" as well as all other terms referenced throughout the Draft Guidance (e.g., "clinically significant", "common", etc.) as part of the proposed rule. Without clear definitions of these terms, we believe that labeling will be based on individual definitions about what is "important" and "clinically significant", and will ultimately result in less rather than more consistency across different drugs and drug classes. Additionally, use of the term "serious" in this context is misleading, as, per the regulatory definition, it should not be used to imply clinical intensity.

   Merck Recommendation:
   Merck recommends that FDA institute regulatory definitions of terms and, in order to ensure consistency, that established internationally-agreed definitions be utilized. If FDA decides, after further review, to use terms not previously defined, all of these terms should be clearly defined in the Glossary. The terms should be used uniformly across all products to avoid ambiguity in individual interpretation (e.g., CIOMS III definitions for frequency, ICH definitions of adverse event, adverse reaction, and serious, etc.). Any newly defined term may not be able to be implemented immediately in labeling since the term will have had to first be included in the definitions used for the product's clinical trials. Merck also recommends the term "serious" be replaced in this context with a more appropriate term, such as "severe", to avoid confusion with the regulatory definition of the terms.

3. The Draft Guidance recommends the Overview list the "most commonly occurring adverse reactions". This term requires further clarification since the frequency of adverse events reported spontaneously cannot be accurately assessed.

Merck Recommendation:
Merck recommends this statement be further defined as referring to those adverse reactions reported from clinical trials.

4. The Draft Guidance recommends presentation of adverse reactions most frequently resulting in clinical intervention in the Overview subsection. Presentation of this information would be duplicative to the information already described in the WARNINGS and PRECAUTIONS sections of the labeling, sections where any adverse reaction requiring clinical intervention would already be described.

   Merck Recommendation:
   Merck recommends that this information continue to be maintained in the appropriate labeling sections with cross references to these sections for more detailed discussions of the adverse reactions provided in the ADVERSE REACTIONS section.

5. The Draft Guidance, in this same section, also provides an example of concomitant medications as a medication to treat an adverse reaction symptom. This terminology will likely be confusing to the health care provider, as the term is usually reserved for medications taken at the same time as the pharmaceutical or biological product, rather than to treat any side effects of the suspect product; e.g., concomitant administration of vaccines or multiple pharmaceutical products used to treat a specific condition.

   Merck Recommendation:
   Merck recommends the term "concomitant" be deleted from the example.

Section B. Discussion of Adverse Reactions Information — Content and Format

1. *Statement Concerning the Significance of Adverse Reaction Data Obtained from Clinical Trials*
   The Draft Guidance recommends addition of a standard statement explaining the significance of adverse reaction data from clinical trials. Merck does not agree as this does not add value to this section and could detract from the actual adverse reaction data presented in this section by questioning the validity of data added from post approval spontaneous reports.

   Merck Recommendation:
   Merck recommends that this introductory paragraph either be deleted or considered to be optional text.

2. *Description of Data Sources*
   The Draft Guidance recommends addition of a description of data sources as an introductory paragraph for the results of clinical studies along with a rationale for not adding all terms. Merck agrees with the proposal to add an introductory paragraph; however, adding a rationale for not including all terms is unnecessary and would lead to questions and concerns from the health care provider regarding the limitations of the data presented.

   Merck Recommendation:
   Merck recommends limiting this introduction to a description of the data included.

3. Use of terms such as "critical exclusions" and "unusual components" of the database without definition of these terms could lead to ambiguity in deciding what information to include resulting in divergent information depending on individual interpretation.

   Merck Recommendation:
   As mentioned previously, if FDA decides, after further review, to use terms not previously defined, Merck recommends they should all be clearly defined in the Glossary.

4. *Commentary and Elaboration on Tabular Data*
   Discussion of Clinically Important Adverse Reactions
   As stated above, providing additional data in this section about the more clinically important adverse reactions listed in the table would result in duplicating information already described in the WARNINGS and PRECAUTIONS sections. The ADVERSE REACTIONS section should generally only contain the reaction observed, supplemented by appropriate incidence estimates if available from clinical trials.

   Merck Recommendation:
   Merck recommends that only cross references to the appropriate sections (e.g., WARNINGS or PRECAUTIONS) be included with the term rather than providing additional information about the term in this section.

5. **Dose-Response Information**
   The Draft Guidance recommends describing the manner in which dose response was investigated. Although describing adverse reactions that exhibit a dose response is appropriate, describing the manner in which dose response was investigated will provide no additional value.

   Merck Recommendation:
   Merck recommends deletion of the phrase regarding the manner in which the dose response was investigated.

6. *Presentation of Less Common Events*
   This section discusses the addition of "significant" adverse reactions which occur less frequently than the frequency cut-off for inclusion in the table.

   Merck Recommendation:
   If FDA decides, after further review, to use terms (e.g., significant) not previously defined, Merck recommends they should be clearly defined in the Glossary.

7. This section also includes specific examples for infrequent but "serious" terms. Merck does not agree with inclusion of examples of adverse event terms as it could be misinterpreted to assume these terms must be included whenever a report is received, regardless of relationship to the product.

   Merck Recommendation:
   Merck recommends that specific examples of such adverse event terms or diagnoses not be included in the guidance since they could be misleading.

8. As stated previously in Section A.2, use of the term "serious" in this context is misleading, as, per the regulatory definition, it should not be used to imply clinical intensity.

   Merck Recommendation:
   Merck recommends this term be replaced with a more appropriate term, such as "severe", to avoid confusion with the regulatory definition of the terms.

9. The Draft Guidance specifies "if numbers of reports are cited, the period of observation should be stated". Merck does not agree as it would be difficult to assure accuracy of these numbers based on post-marketing reporting and could be interpreted by the reader as providing trend information regarding the specific adverse event.

   Merck Recommendation:
   Merck recommends that the statement regarding the observation period be deleted.

Organizing and Presenting Adverse Reaction Data in a Table

Percentages
The Draft Guidance specifies that "Adverse reaction rates should ordinarily be rounded to the nearest integer." Merck does not agree as this may not provide adequate information as compared to placebo or active control, especially if the terms listed in the table are all occurring at a relatively low rate. For example, for adverse reaction rates occurring at a rate of I to 2% and greater than the placebo rate, more useful information would be provided if the percentages were rounded to the nearest tenth of a percent.

Merck Recommendation:
Merck recommends that this section be amended to allow flexibility in the presentation of the percentages (i.e., integers vs tenths), depending on the specific product's adverse reaction rates. Additionally, it would be appropriate in this section to allow the presentation of adverse reaction rates in terms of patient years or months of exposure instead of crude rates, i.e., the number of adverse reactions per the number of patients randomized in the clinical studies. This would permit a fairer comparison of rates between studies of different duration, and would provide a vehicle for more meaningful pooling of rates across studies.

Significance Testing
The Draft Guidance indicates that significance testing results may be included if the results provide "critically useful information and are based on a prespecified hypothesis...."

Merck Recommendation:
Merck recommends that any significance testing must be based on a pre-defined hypothesis and limited to only include adverse reactions of specific interest for the product. Otherwise significance testing should neither be performed for adverse reactions nor included within the ADVERSE REACTIONS section of labeling.

Presenting Data in the ADVERSE REACTIONS Section of the Labeling

Rare, Serious Events

The Draft Guidance provides examples of serious adverse events and proposes these events be included in labeling even if there are only one or two reported events. As mentioned previously, Merck does not agree with inclusion of examples of adverse event terms as it could be misinterpreted to assume these terms must be included whenever a report is received, regardless of relationship to the product.

Merck Recommendation:
Merck recommends that the reference to examples of these adverse event terms or diagnoses be deleted, the title be revised to "Rare Adverse Events", and the use of the term "serious" be replaced with a more appropriate term, such as severe.

Merck also recommends that the statement concerning inclusion of rare adverse events in labeling "...even if there are only one or two reported events." be clarified to specify addition of such terms if these are suspected reactions (i.e., events not causally related to the drug should be excluded).

Determining Adverse Reaction Rates

The Draft Guidance recommends the "rate of an identified adverse reaction should ordinarily be derived from all adverse events..." If only adverse reactions (i.e., those shown to be related to drug therapy) are to be included in this section of the labeling, why should the rate be determined based on all adverse events (i.e., including those reported but not determined to be drug-related)?

Merck Recommendation:
Merck recommends that the rate be determined based only on drug relationship. Additionally, the paragraph and title should be modified to specify adverse reaction rates determined from clinical trials.

Updating the ADVERSE REACTIONS Section of Labeling

Sources

The paragraph mentions safety issue documents from consulting CBER or CDER Divisions (in CBER, Office of Biostatistics and Epidemiology; in CDER, Office of Postmarketing Drug Risk Assessment).

Merck Recommendation:
Merck recommends the term "safety issue documents" be further defined and not limited to documents issued from only the two FDA departments mentioned.

Inconsistent or Outdated Information

The Draft Guidance recommends labeling be reviewed to ensure consistency with newly acquired data from controlled clinical trials or spontaneous reports and to "...seek out any defects in labeling that may have accumulated with time...." The deletion of outdated information needs to be explained more clearly as it would be difficult to justify deletion of safety information about the product from either the earlier studies or post marketed use and could potentially put the

company at risk for liability for deletion of what could be or had been considered important safety information.

Merck Recommendation:
Merck recommends the title of this section be revised to "Review of Safety Information" to more accurately reflect the information provided. Merck also recommends a more detailed explanation of the phrase "seek out any defects in labeling that may have accumulated with time".

Further, Merck recommends the sentence discussing reliable new adverse reaction data be revised to "When there is reliable new adverse reaction information (either overall information or data relevant to a particular adverse reaction) that is either inconsistent with or provides additional information regarding the adverse reaction section or a particular adverse reaction, the section should be appropriately updated to reflect new information. If this information also pertains to other sections of the labeling (e.g., WARNINGS or PRECAUTIONS sections) those sections should also be updated as appropriate at the same time".

Glossary
The Glossary defines several, but not all, terms introduced in this document. Merck agrees with the concept of inclusion of a Glossary but it should include all appropriate terms.

Merck Recommendation:
Merck recommends that all terms listed throughout the Draft Guidance as requiring definition be included in this section. FDA should ensure consistency with internationally-accepted terminology.

Merck also recommends, in Footnotes 6 and 7, reference should be made to ICH E2A rather than ICH E8.

CONCLUSIONS

In summary, Merck commends the Agency for developing a document designed with the intent to provide guidance across the industry resulting in uniform content and format of the ADVERSE REACTIONS section of prescription labeling. As stated earlier, Merck anticipates that this document will be a part of, and implemented with, the proposed regulation on the Content and Format of Prescription Labeling rather than implemented separately. This approach would provide the most efficient and effective utilization of resources both within the FDA and the pharmaceutical industry.

Merck welcomes the opportunity to provide comments on the proposed Guidance for Industry on the Content and Format of the ADVERSE REACTIONS Section of Labeling for Human Prescription Drugs and Biologics and hope that our comments will be useful in this endeavor.

Please direct any correspondence concerning these comments to Dr. Bonnie Goldmann (610-397-2383).

Sincerely yours,

Dennis M. Erb for,
Bonnie J. Goldmann, M.D.
Vice President
Regulatory Affairs

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